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(54) Title: A METHOD FOR PREPARING RESINATES

(57) Abstract: A highly productive and environmentally friendly method of loading pharmaceutically active substances onto ion exchange resins using a water miscible or water-immiscible solvent is disclosed.

## A METHOD FOR PREPARING RESINATES

### BACKGROUND OF THE INVENTION

It is well known in the art that using a complex formed between a  
5 polymeric material and an active substance can be beneficial. Such  
benefits can include changes in the release rate of drugs, taste masking of  
bitter drugs, control of the site of administration of drugs, control of the  
release of flavor substances, and stabilization of unstable substances.

10 The preparation of an active substance/ion exchange resin complex is  
called loading. The ion exchange resins complexed with the active  
substance are called resinates. The methods for loading have been varied,  
but in many cases are either problematic or limited in their application.

15 The typical method for loading active substances onto an ion  
exchange resin is to dissolve an acidic or basic, ionizable active substance  
in water, and then mix it with a suitable ion exchange resin. See,  
US2,990,332. The active substance is absorbed into the resin by the  
mechanism of ion exchange. The extent of loading will depend on several  
20 factors, including the rate of diffusion, the equilibrium constant,  
temperature, and the presence of other ions. The water is then removed by  
filtration, and the ion exchange resin dried by heating. As a general rule,  
anion exchange resins are useful for the loading of acidic substances, and  
cation exchange resins are useful for loading basic substances.

25 The need to dissolve the active substance to be loaded can lead to  
very large volumes of solution if the active substance has poor solubility in  
the loading medium. This leads to very low productivity in a commercial  
scale process. To overcome this problem, water miscible organic co-  
30 solvents such as ethanol are frequently used to increase the solubility and  
to reduce the total volume of solution. Introduction of these co-solvents

into the process can add significant cost, because they are typically not recovered. They can increase the amount of hazardous waste generated, and introduce processing problems related to flammability and toxicity.

5        In the currently used commercial processes for making the resinate  
of active substances, said active substance is loaded onto a powdered, anion  
or cation ion exchange resin. The loading is performed in a predominantly  
aqueous system, whereby the active substance becomes immobilized on the  
resin by reaction with the functional groups of the resin. Use of an  
10      aqueous system for the loading has the disadvantage that the resulting  
slurry has to be dewatered and dried. This is currently achieved in a  
number of different ways, e.g., dewater in a decanter, and then dry in a  
vacuum dryer; or evaporate the water directly from the slurry in a vacuum  
distillation apparatus; and evaporate the water directly from the slurry  
15      using a spray dryer. There are problems associated with each of these  
methods. The decanter operation is made difficult because the ion  
exchange resin contains a significant fraction of very fine particles  
(<40 micron), and wet-cakes from such decanters can still contain >60%  
water by weight. The spray dryer and vacuum distillation operations are  
20      energy wasteful because all the water is removed by conversion to water  
vapor. Also, these methods can lead to particle agglomeration. Avoidance  
of these problems by using typical organic solvents leads to problems of  
toxicity from the residual solvent, safety problems from flammability, and  
environmental problems from vapor emissions and waste disposal.

25

The use of non-aqueous solvents as media for ion exchange reactions  
has been reported. See "*Ion Exchange Resins*" by Robert Kunin, p. 310,  
published by Robert E. Krieger Publishing Co, 1990. However, reaction  
times are reported to be very long for non-swelling solvents. Further, the  
30      solvents typically used are not optimum for industrial scale because they

are flammable, or toxic, or difficult to remove efficiently, or difficult to reuse, or environmentally unacceptable, or high cost.

Many drug substances are hydrophobic and are poorly soluble in water. While this can be somewhat advantageous for absorption from solution into the gastrointestinal system, the actual dissolution of such drugs into physiological fluids can be very inefficient. This can result not only from a low solubility, but also a low rate of dissolution. This low rate of dissolution is itself the result of poor wettability of the hydrophobic solid, and the thermodynamic barrier caused by high crystal lattice energy which is difficult to overcome with water. This poor dissolution into physiological fluids can result in very poor and/or variable bioavailability of the drugs. Methods to improve the dissolution can thereby improve bioavailability.

For example, when nicotine is formulated into chewing gum and lozenges it is first loaded onto a cation exchange resin which has the effect of controlling the release rate of the nicotine during chewing or sucking in the mouth. Such complexes of nicotine with ion exchange resins are the subject of GB1325011. In agriculture it is used as a pesticide; and it is formulated as the nicotine sulfate salt in water, at a 40% concentration.

A number of solutions have been explored, including grinding the drug to very small particle size (WO99/30687) and supplying it as a solution in oils (EP0306236B1). Each of these techniques has disadvantages. For example, not all drugs can be ground to very fine particle size due to low melting point or heat sensitivity. Dissolution in oils or dispersion in other matrices severely restricts the formulation options. There is a need for a method to improve dissolution that does not suffer these disadvantages.

The use of ion exchange resins to improve the rate of dissolution of weakly ionic compounds was reported by Irwin. See, Irwin, et al, Drug Deliv. and Ind. Pharm, 16(6), 883 (1990). Irwin observed faster dissolution of mefenamic acid from a powdered, strong base anion exchange resin 5 when compared to a solid suspension. The loading method used by Irwin employed an aqueous medium as known to those skilled in the art.

Thus, there is a need in the art for an active ingredient loading method that is environmentally friendly, safe, low cost, and capable of high 10 productivity. There is also need for a method that improves the dissolution of poorly soluble drugs that is not limited by melting point or temperature sensitivity, and is compatible with most existing formulation methods. Applicants have surprisingly discovered a method that meets these needs and is applicable to a variety of active substances having varying 15 solubilities.

The following terms have the following meanings herein:

The term "solubility," as used herein, means solubility as defined in the US Pharmacopoeia, 24, pg. 10. For the purposes of this invention the descriptor 'poorly soluble' will be used to describe substances that are very slightly soluble or practically insoluble in water by the USP definition. This solubility is <1 part of solute per 1000 parts of solvent. The descriptor 'soluble' will be used to describe substances with a solubility >1 part solute 20 per 1000 parts solvent.

25

The term "water retention capacity" as used herein is used to describe the maximum amount of water that an ion exchange resin can retain within the polymer phase and in any pores. (ASTM D2187: Standard Test Methods for Physical and Chemical Properties of Particulate 30 Ion Exchange Resin. Test Method B: Water Retention Capacity)

The term "resinate," as used herein, means an active substance/resin complex.

5 The terms "loaded" and "loading" as used here-in mean the preparation of a resinate. The amount of loading means the amount of active substance incorporated into the resin to form a resinate.

Further, ion exchange resins are characterized by their capacity to exchange ions. This is expressed as the "Ion Exchange Capacity." For cation exchange resins the term used is "Cation Exchange Capacity," and 10 for anion exchange resins the term used is "Anion Exchange Capacity." The ion exchange capacity is measured as the number equivalents of an ion that can be exchanged and can be expressed with reference to the mass of the polymer (herein abbreviated to "Weight Capacity") or its volume (often abbreviated to "Volume Capacity"). A frequently used unit for weight 15 capacity is "milliequivalents of exchange capacity per gram of dry polymer." This is commonly abbreviated to "meq/g."

Ion exchange resins are manufactured in different forms. These forms can include spherical and non-spherical particles with size in the 20 range of 0.001mm to 2mm. The non-spherical particles are frequently manufactured by grinding of the spherical particles. Products made in this way typically have particle size in the range 0.001mm to 0.2mm. The spherical particles are frequently known in the art as 'Whole Bead.' The non-spherical particles are frequently known in the art as 'Powders.'

25

#### STATEMENT OF THE INVENTION

The present invention relates to a method for preparing a resinate comprising the steps of:

- a. blending a poorly water soluble active substance with a resin 30 and a solvent selected from the group consisting of water, a water

miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;

5           b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.

The present invention further relates to a method for preparing a resinate comprising steps of:

10           a. blending a water soluble active substance with a resin and a solvent selected from the group consisting of a water miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;

15           b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for preparing a resinate comprising the steps of:

20           a. blending a poorly water soluble active substance with a resin for example an ion-exchange resin, and a solvent selected from the group consisting of water, a water miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;

25           b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.

The present invention further relates to a method for preparing a resinate comprising steps of:

- a. blending a water soluble active substance with resin, for example an ion-exchange resin, and a solvent selected from the group consisting of a water miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;
- 5 b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.

10 Said resin may be an ion-exchange resin or an adsorbent resin.

Preferably, said resins are suitable for human and animal ingestion.

15 Ion exchange resins useful in the practice of the present invention include, but are not limited to, anionic exchange resins and cationic exchange resins.

20 Preferred anionic exchange resins include, but are not limited to, styrenic strongly basic anion exchange resins with a quaternary amine functionality having a weight capacity of 0.1 to 15 meq/g, and styrenic weakly basic anion exchange resins with a primary, secondary, or tertiary amine functionality having a weight capacity of 0.1 to 8.5 meq/g, and acrylic or methacrylic strongly basic anion exchange resins with a quaternary amine functionality having a weight capacity of 0.1 to 12 meq/g, and acrylic or methacrylic weakly basic anion exchange resins with a primary, secondary, or tertiary amine functionality having a weight capacity of 0.1 to 12 meq/g, and allylic and vinylic weakly basic anion exchange resins with a primary, secondary, or tertiary amine functionality having a weight capacity of 0.1 to 24 meq/g, that are suitable for human  
25 and animal ingestion.

30

Most preferred anionic exchange resins include, but are not limited to, styrenic anion exchange resins with quaternary amine functionality with weight capacity of 0.1 to 6 meq/g and acrylic anion exchange resins with tertiary amine functionality with weight capacity of 0.1 to 12 meq/g,  
5 that are suitable for human and animal ingestion.

Preferred cationic exchange resins include, but are not limited to, styrenic strongly acidic cation exchange resins with sulfonic or phosphonic acid functionalities having a weight capacity of 0.1 to 8 meq/g; and styrenic  
10 weakly acidic cation exchange resins with carboxylic or phenolic acid functionalities having a weight capacity of 0.1 to 8.5 meq/g; and acrylic or methacrylic weakly acidic cation exchange resins with a carboxylic or phenolic acid functionality with a weight capacity of 0.1 to 14 meq/g, that are suitable for human and animal ingestion.

15

Most preferred cationic exchange resins include, but are not limited to, styrenic weakly acidic cation exchange resin with a phenolic functionality with a weight capacity of 0.1 to 8.5 meq/g; and a styrenic strongly acidic cation exchange resin with a sulfonic acid functionality with  
20 weight capacity of 0.1 to 8 meq/g, or a methacrylic weakly acidic cation exchange resin with a carboxylic acid functionality with weight capacity of 0.1 to 12 meq/g.

Ion exchange resins useful in this invention have a moisture content  
25 between 0% and the water retention capacity of said resin.

Ion exchange resins useful in this invention are in powder or whole bead form.

Strongly acidic and weakly acidic cation exchange resins useful in the practice of the present invention are in the acid form or salt form or partial salt form.

5        Strongly basic anion exchange resins useful in this invention are in the salt form.

Weakly basic anion exchange resins useful in this invention are in the free-base form or salt form.

10      Adsorbent resins useful in the practice of this invention include, but are not limited to, carbonaceous adsorbents, acrylic adsorbents and phenol-formaldehyde adsorbents. Preferred adsorbents useful in the practice of this invention are carbonaceous adsorbents, acrylic adsorbents, and  
15      phenol-formaldehyde adsorbents.

More preferred adsorbent resins useful in the practice of this invention are acrylic adsorbent resins.

20      Preferred adsorbent resins useful in this invention are in powder or whole bead form.

25      The water soluble or poorly water soluble active substances useful in the practice of the present invention have acidic or basic ionizable groups.

Preferred poorly water soluble active substances include, but are not limited to, indomethacin, salicylic acid, ibuprofen, sulindac, piroxicam, naproxen, timolol, pilocarpine, acetylcholine, dibucaine, thorazine,  
30      promazine, chlorpromazine, acepromazine, aminopromazine, perazine,

prochlorperazine, trifluoroperazine, thioproperazine, reserpine, deserpine, chlorprothixene, tiotixene, haloperidol, moperone, trifluorperidol, timiperone, acetaminophen, droperidol, pimozide, sulpiride, tiapride, hydroxyzine, chlordiazepoxide, diazepam, propanolol, metoprolol, pindolol,  
5 imipramine, amitryptyline, mianserine, phenelzine; iproniazid, amphetamines, dexamphetamines, fenproporex, phentermine, amfepramone, pemoline, clofenciclan, cyprodeneate, aminorex, mazindol, progabide, codergoctine, dihydroergocristine, vincamone, citicoline, physostigmine, pyritinol, meclofenoxate, lansoprazole, nifedipine,  
10 risperidone, clarithromycin, cisapride, nelfinavir, midazolam, lorazepam, ciprofloxacin, quinapril, isotretinoin, valacyclovir, acyclovir, delavirdin, famciclovir, lamivudine, zalcitabine, osteltamivir, abacavir, prilosec, omeprazole, prozac, zantac, and lisinopril.

15 The more preferred poorly water soluble pharmaceutically active substances include, but are not limited to indomethacin, lansoprazole, nifedipine, risperidone, clarithromycin, cisapride, nelfinavir, midazolam, lorazepam, ciprofloxacin, quinapril, and isotretinoin.

20 The most preferred poorly water soluble pharmaceutically active substances are indomethacin, nelfinavir, and midazolam.

Preferred water soluble active substances include, but are not limited to, acarbose, acyclovir, alendronate, amantadine, 4-aminopyridine, amphotericin B, azithromycin, aztreonam, ceftriaxone, cefuroxime,  
25 cromalyn, deferriprone, dextromethorphan, diclofenac, didanosine, etidronate, famiciclovir, foscarnet, ganciclovir, indinavir, metformin, nedocromil, neostigmine, nicotine, olpadronate, pamidronate, pyridostigmine, residronate, rimantadine, salmeterol, stavudine, ticarcillin, tiludronate, valaciclovir, zalcitabine, zanamavir and zidovudine.

More preferred water soluble active substances include, but are not limited to, acyclovir, 4-aminopyridine, azithromycin, deferriprone, dextromethorphan, diclofenac, didanosine, famiciclovir, foscarnet, ganciclovir, indinavir, nedocromil, nicotine, pyridostigmine, stavudine, 5 ticarcillin, tiludronate, valaciclovir, zalcitabine, zanamavir and zidovudine.

The most preferred water soluble active substance is nicotine.

Nicotine useful in the practice of the present invention includes, but is 10 not limited to, that derived from the extraction of nicotine from the tobacco plant *Nicotiana tobacum*. It finds great use in the pharmaceutical and agricultural industries. In the pharmaceutical industry it is extensively used in smoking cessation formulations. In this use the nicotine can be administered in the form of lozenges, chewing gum, and inhalers.

15

The preferred nicotine useful in the practice of the current invention is nicotine that has an assay greater than 90% by weight.

20 The more preferred nicotine useful in the practice of the current invention is nicotine that has an assay greater than 95% by weight.

The most preferred nicotine useful in the practice of the current invention is nicotine that meets the purity specifications prescribed in the US PharmacopeiaUSP24, p1179.

25

Vitamins useful in the practice of the present invention include, but are not limited to, A (poorly water soluble), C (water soluble), E (poorly water soluble), and K (water soluble).

30 An active substance for use in the preparation of a resinate as described above may be a naturally-occurring or a synthetic material. A

said naturally occurring material may be an extract from a botanical material. Preferred extracts include nutraceutical and biologically active extracts of botanical materials and flavours and fragrances.

5        Nutraceutical and Biologically active extracts of botanical materials that are useful include, but not limited to, anti oxidants such as phytophenols obtained from extracts of rosemarinus officinalis, anti fungal and anti infective agents such as extracts of oregano and Cocos mucifera, carminatives such as extracts of peppermint, malaria therapeutics such as  
10      artemisinins from extracts of Artemesia annua, anxiolytic agents such as Kavalactones from Piper methysticum (e.g. kava root), ACE and AchE enzyme inhibition agents such as extracts of ginseng and salvia, cytotoxic agents such as extracts of cowbane and Bullatacinone obtained from extract of Annona bullata, analgesics such as extracts of Mentha piperita,  
15      anticeptics, such as extracts of Mentha piperita, pheromone such as heptan-2-one from extract of Arum maculatum, sedatives such as linalool from extract of Coriandum sativum, vascodilators such as theobromine from the extract of Theobroma cacao and histamine from musa sapientum (banana plant), anaesthetic such as Aconitine from the extract of  
20      Aconitum napellus.

Flavours and fragrances that are useful include, but not limited to, menthol from the extract of Mentha piperita, gamma-nonalactone from Prunus persica, Linalool from extracts of Coriandum sativum, geranyl acetate from extract of Pelagonium odoratissimum, Jasmone from extracts of Jasminum officinalis, extract of rose flower, cinnamaldehyde from extracts of cinnamon, extracts of vanilla, whole extract of peppermint and spearmint.  
25

Flavors and fragrances which may be useful and can be obtained synthetically include, but are not limited to, vanillin, methyl salicylate, thymol and ethyl vanillin.

5 An active substance for use in the preparation may be a derivative of a botanical extract.

Preferred methods of extracting flavours and fragrances (and other materials which may be used in the preparation of active materials) for use  
10 in the preparation of resonates are described in EP 94301199.9, WO95/26794 and WO98/45013 and the contents of the aforementioned are incorporated herein by reference.

15 The preferred solvents useful in the practice of the present invention are selected from the group consisting of water, water miscible solvents, water immiscible solvents and mixtures thereof.

Water miscible solvents useful in the practice of the present invention include, but are not limited to, methanol, ethanol, isopropanol, n-  
20 propanol, acetone, dimethylformamide, tetrahydrofuran, dimethyl sulfoxide, dimethyl ether, and acetic acid.

The preferred water miscible solvents are ethanol, isopropanol, n-propanol, and dimethyl ether.

25

The most preferred water miscible solvent is ethanol.

Water immiscible solvents useful in the practice of the present invention include, but are not limited to hydrocarbons, halogenated  
30 hydrocarbons, ethers, ketones, and esters having boiling points, at atmospheric pressure between 100°C and -100°C.

The preferred water immiscible solvents are fluorinated hydrocarbon solvents. In the method, a said fluorinated hydrocarbon solvent is preferably in the liquid state when in contact with the active substance.

5 A preferred fluorinated hydrocarbon is a C<sub>1</sub> to C<sub>4</sub> fluorinated hydrocarbon.

10 The C<sub>1</sub> to C<sub>4</sub> fluorinated hydrocarbon may be non-chlorinated. Preferably, it comprises one or more carbon, fluorine and hydrogen atoms only. Preferably, said fluorinated hydrocarbon is a C<sub>1</sub> to C<sub>3</sub>, more preferably, a C<sub>1</sub> to C<sub>2</sub> fluorinated hydrocarbon. Especially preferred is a C<sub>2</sub> fluorinated hydrocarbon.

15 Said fluorinated hydrocarbon may include up to 10, preferably up to 8, more preferably up to 6, especially up to 4, fluorine atoms.

Said fluorinated hydrocarbon is preferably aliphatic. It is preferably saturated.

20 Said fluorinated hydrocarbon may have a boiling point at atmospheric pressure of less than 20°C, preferably less than 10°C, more preferably less than 0°C, especially less than -10°C. The boiling point may be greater than -90°C, preferably greater than -70°C, more preferably greater than -50°C.

25

Preferred water immiscible solvents are:

trifluoromethane (CF<sub>3</sub>H);

fluoromethane (CH<sub>3</sub>F);

difluoromethane (CF<sub>2</sub>H<sub>2</sub>);

30 1,1-difluoroethane (CF<sub>2</sub>HCH<sub>3</sub>);

1,1,1-trifluoroethane (CF<sub>3</sub>CH<sub>3</sub>);

1,1,1,2-tetrafluoroethane ( $\text{CF}_3\text{CFH}_2$ )  
pentafluoroethane ( $\text{CF}_3\text{CF}_2\text{H}$ );  
1,1,1,2,2-pentafluoropropane ( $\text{CF}_3\text{CF}_2\text{CH}_3$ );  
1,1,1,2,3-pentafluoropropane ( $\text{CF}_3\text{CFHCFH}_2$ );  
5 1,1,1,2,2,3-hexafluoropropane ( $\text{CF}_3\text{CF}_2\text{CFH}_2$ );  
1,1,1,2,3,3-hexafluoropropane ( $\text{CF}_3\text{CFHCF}_2\text{H}$ );  
1,1,1,3,3,3-hexafluoropropane ( $\text{CF}_3\text{CH}_2\text{CF}_3$ );  
1,1,2,2,3,3-hexafluoropropane ( $\text{CF}_2\text{HCF}_2\text{CF}_2\text{H}$ );  
1,1,1,2,2,3,3-heptafluoropropane ( $\text{CF}_3\text{CF}_2\text{CF}_2$ );  
10 1,1,1,2,3,3,3-heptafluoropropane ( $\text{CF}_3\text{CFHCF}_3$ );

Tetrafluorethane is an especially preferred solvent with 1,1,1,2-tetrafluoroethane ( $\text{CF}_3\text{CFH}_2$ ), also known as TFE, being most preferred. This solvent has a boiling point of -26.5°C at atmospheric pressure, is of  
15 low toxicity, is non-flammable, and is non ozone depleting.

Said solvent used in the preparation of a said resinate may include a fluorinated hydrocarbon solvent (especially TFE) as described together with one or more co-solvents. Said solvent may include less than 20wt%,  
20 preferably less than 15wt%, more preferably less than 10wt% of co-solvent.

A said co-solvent may be selected from: a C<sub>2</sub>-6 hydrocarbon such as an alkane or cycloalkane with alkanes such as ethane, n-propane, i-propane, n-butane and i-butane being especially preferred; and  
25 hydrocarbon ethers, particularly dialkylethers such as dimethylether, methylethylether and diethyl ether. In other embodiments, said co-solvent may be polar, for example having a dielectric constant, at 20°C, of greater than 5. Such co-solvents may be selected from:

30 amides, especially N,N'-dialkylamides and alkylamides, with dimethylformamide and formamide being preferred; sulphozides, especially

dialkyl sulphoxides, with dimethylsulphoxide being preferred; alcohols, especially aliphatic alcohols for example alkanols, with methanol, ethanol, 1-propanol and 2-propanol being preferred; ketones, especially aliphatic ketones, for example dialkyl ketones, with acetone being especially preferred; organic acids, especially carboxylic acids with formic acid and acetic acid being preferred; carboxylic acid derivatives, for example anhydrides, with acetic anhydride being preferred; cyanide derivatives, for example hydrogen cyanide and alkyl cyanides, with methyl cyanide and liquefied anhydrous hydrogen cyanide being preferred; ammonia; sulphur containing molecules including sulphur dioxide, hydrogen sulphide and carbon disulphide; inorganic acids for example hydrogen halides with liquefied anhydrous hydrogen fluoride, chloride, bromide and iodide being preferred; nitro derivatives, for example nitroalkanes and nitroaryl compounds, with nitromethane and nitrobenzene being especially preferred.

In a preferred embodiment when a fluorinated hydrocarbon solvent is used, substantially no co-solvent of the types described is used.

The preferred range of ratios of ion exchange resin to solvent is 1:1 to 1:1000, the more preferred range is 1:1.5 to 1:100, and the most preferred range is 1:2 to 1:5.

Preferably, the loading of active substance in the resinate of the present invention is 1-100% of the ion exchange capacity of the resin, more preferably it is 5-100% of the ion exchange capacity of the resin, and most preferably it is 10-100% of the ion exchange capacity of the resin.

The preferred pressure range for the practice of the present invention is 5 to 35,000 kPascals, the more preferred range is 100 to 5000 kPascals, and the most preferred range is 350 to 700 kPascals.

The preferred temperature range for the practice of the present invention is 10°C to 100°C, the more preferred range is 0°C to 80°C, and the most preferred range is 5°C to 30°C.

5 Preferably, the time to prepare a resinate of the present invention is from 1 second to 48 hours, more preferably from 5 minutes to 12 hours, and most preferably from 5 minutes to 8 hours.

10 Preferably, a said method of preparing a resinate includes a step of separating a resinate comprising active substance/resin from solvent. This may suitably be done by filtration and/or vapourization of solvent. Thus, preferably the method includes the step of isolating the resinate, suitably in a solid form.

15 The invention extends to a method of preparing a resinate comprising the steps of:

20 (a) blending an active substance with a resin as described herein and a solvent as described herein (preferably a fluorinated hydrocarbon solvent as described herein) to form an active substance/resin/solvent mixture; and

(b) separating a resinate comprising active substance/resin from solvent.

25

Said resinate is preferably formed into units comprising predetermined amounts of said active substance.

30 It may be difficult, in some cases, to remove all of the solvent used in the preparation of a resinate from the resinate itself and, accordingly, the resinate may be contaminated with a trace of solvent. Therefore, the

invention extends a resinate comprising an active substance in combination with a resin, wherein the resinate includes a trace (e.g. less than 1wt%, preferably less than 0.5 wt%, especially less than 0.1wt% based on the total weight of resinate) of solvent.

5

Where a fluorinated hydrocarbon (e.g. tetrafluoroethane as described herein) is used in the preparation of a resinate, the invention extends to a resinate comprising an active substance in combination with a resin, wherein the resinate includes a trace (e.g. less than 1wt%, preferably less than 0.5wt%, especially less than 0.1 wt% based on the total weight of resinate) of a fluorinated hydrocarbon (e.g. 1,1,1,2-tetrafluoroethane).

A resinate as described herein may have many potential applications. Preferably, it is included in a formulation. Thus the 15 invention extends to a formulation comprising a resinate as described herein. The formulation preferably includes at least 0.25 wt% of resinate. The formulation preferably includes 0.5 to 99 wt%, preferably 5 to 90wt% of resinate.

20 A said formulation may include said resinate in combination with another solid or liquid. The formulation may include at least 1 wt%, preferably at least 5wt%, more preferably at least 10wt%, especially at least 30wt% of said other solid or liquid.

25 Said solid or liquid may be a carrier, excipient or diluent.

The invention further extends to a method of preparing a formulation which comprises contacting a resinate as described herein with another solid or liquid.

Preferably, in a method of preparing a resinate as described herein, at least 0.5 kg, especially at least 1kg, of an active substance is blended with solvent. The active substance and solvent may be blended for a time of less than 2000 hours preferably less than 1000 hours, more preferably 5 less than 500 hours, especially less than 100 hours.

While Example 1 surprisingly illustrates that a poorly soluble drug can be loaded onto an ion exchange resin with less water than is required to completely dissolve said drug, the loading process takes about 2 hours 10 and the mixture must be dewatered.

However, the addition of a water-immiscible or water miscible solvent as described hereinabove reduces the loading time to between 1 minute and 20 minutes, and eliminates the need to dewater the mixture. 15 For example, in a preferred embodiment of the invention, the amount of water required is such that it does not exceed the water retention capacity of the ion exchange resin. In this way there is no separate water phase in the mixture. Because of the property of ion exchange resins to absorb water up to the water retention capacity the water can either be present in 20 the ion exchange resin at the start of the process, or added as a separate ingredient to the mixture. The water immiscible solvent can be removed from the final mixture either by filtration, or by vaporization. The vaporization can be achieved by using heat, or by reducing the pressure, and providing a heat source to maintain the temperature of the solution 25 between room temperature and the atmospheric pressure boiling point of said solvent. Specifically, the active substance, a suitable hydrated anion or cation exchange resin, and TFE are mixed at a pressure of about 520 kPascals to maintain said TFE in the liquid state. The mixture is stirred at room temperature for between 5 and 20 minutes. During this period the 30 active substance rapidly loads onto the ion exchange resin, such that there is no solid active substance left in the mixture, and the amount of active

substance dissolved in the TFE is insignificantly small. The TFE is then removed by reducing the pressure such that the TFE boils. The TFE vapor can be recovered either by using a condenser at less than the boiling point of the TFE, or by using a compressor and condenser. Both recovery methods are well known in the art. The TFE can then be re-used.

The following non limiting examples illustrate the practice of the present invention.

10      **EXAMPLE 1 – Water-Only Loading of a Poorly Water Soluble Active**

Add 0.5 g of indomethacin, a poorly soluble active substance, and 1.5g of an acrylic anion exchange resin with tertiary amine functionality and a weight capacity between 5.8 and 6.2 meq/g, such as Amberlite IRA67, available from the Rohm and Haas Company, in its fully hydrated state to a 25 ml vial. Add 6 g of water to the mixture, close the vial and shake the mixture. After 2 hours the indomethacin will have disappeared and the ion exchange resin will be yellow. Drain the water from the mixture, to yield the wet resinate.

20      This experiment illustrates the very large reduction in required reaction volume achieved by the invention over the prior art. The solubility of indomethacin in water is 14ppm so that approximately 37kg of water would be required to completely dissolve the amount of indomethacin used in this example. For a commercial scale operation this decrease in required volume would represent a 6000 fold increase in productivity over the prior art.

30      **EXAMPLE 2 – Immiscible Solvent and Prehydrated Resin Loading of a Poorly Water Soluble Active**

Proceed as in Example 1, except add 1.7g of water to the mixture. This is sufficient water to hydrate the ion exchange resin, but not sufficient to form a separate liquid water layer. After stirring for 10minutes stop the stirrer and allow the mixture to stand for a few minutes. It will be noted  
5 that the resin, now yellow in color, will float to the surface, and that there will be no indomethacin on the bottom of the vessel. Carefully remove approximately one half of the TFE as a liquid sample, without including any of the resinate. Remove the TFE from this sample by evaporation. It will be noted that there is no significant solid residue left after the TFE has  
10 been removed. These observations indicate that all the indomethacin loaded onto the resin.

**EXAMPLE 3 – Immiscible Solvent Loading of a Poorly Water Soluble Active**

15 Proceed as in Example 1, except use 7g of dichloroethane. After shaking for 10 minutes, it will be noted that the resin is now yellow, and that there is no solid indomethacin present. This observation indicates the indomethacin loaded onto the ion exchange resin.

20 **EXAMPLE 4 – Immiscible Solvent Loading of a Poorly Water Soluble Active**

Proceed as in Example 1, except use 3.5g of pentane instead of dichloroethane. After shaking for 20 minutes, it will be noted that the resin is now yellow, and that there is no solid indomethacin present. This  
25 observation indicates the indomethacin loaded onto the ion exchange resin

**EXAMPLE 5 – Immiscible Solvent Loading of a Poorly Water Soluble Active**

The same as Example 3, except use 1g of Nelfinivir, 1.4g of water,  
30 and 1.6g of a dried, ground methacrylic weakly acidic cation exchange resin with carboxylic acid functionality with weight capacity between 10.1 and

11.1 meq/g (such as Amberlite<sup>®</sup> IRP64, available from the Rohm and Haas Company).

EXAMPLE 6 – Immiscible Solvent and Prehydrated Resin Loading of a  
5 Poorly Water Soluble Active

In the same equipment as used in Example 2, charge 3g of an acrylic anion exchange resin with tertiary amine functionality and a weight capacity between 5.8 and 6.2 meq/g, such as Amberlite IRA67, available  
10 from the Rohm and Haas Company, in its fully hydrated state, whole bead form. To the same vessel charge 1g of indomethacin. Evacuate the air from the vessel, and then introduce 50g of 1,1,1,2-tetrafluoroethane (TFE) so that at the end of the addition the pressure is approximately 520 kPascals and the temperature is 20°C, such that the TFE is in the liquid  
15 state. Stir the mixture at room temperature for 10 minutes. During this period the resin will change to a yellow color, indicating indomethacin loading. Reduce the pressure in the loading vessel by venting it to the atmosphere to remove the TFE. There remains a water-wet resinate, that is indomethacin loaded onto the anion exchange resin.

20

EXAMPLE 7 – Immiscible Solvent Only Loading Of A Poorly Water Soluble Active

Proceed as in Example 6, except dry the resinate in a vacuum oven at 60°C for 4 hours.

25

EXAMPLE 8 – Miscible Solvent and Water (Due To Hydrated Resin) Loading Of A Poorly Water Soluble Active

Prepare a solution of 1g of indomethacin in 200ml of 50% aqueous ethanol. To this add 3g of an acrylic anion exchange resin with tertiary  
30 amine functionality and a weight capacity between 5.8 and 6.2 meq/g (such as Amberlite IRA67, available from Rohm and Haas Company,

Philadelphia, Pennsylvania) in its fully hydrated state, whole bead form. Shake the mixture overnight at room temperature. During this period the yellow solution will lose most of its color, and the resin will become yellow. Drain the solution from the mixture, and analyze it for indomethacin using 5 a uv-vis spectrometer at a wavelength of 318nm, such as described in US Pharmacopoeia, USP24 p. 874. The analysis will indicate approximately 0.1g of the indomethacin was left in solution, and did not load onto the resin.

10 **EXAMPLE 9 – Miscible Solvent Loading of a Poorly Soluble Active**

The same as Example 1 except that instead of adding water, add 2.5g of water and 2.5g of ethanol. The indomethacin will load within 2 hours. The supernatant at the end of the experiment will contain 15 approximately 0.003g of indomethacin that did not load.

**EXAMPLE 10—Immiscible Solvent Loading Of A Water Soluble Active**

Construct equipment comprising a 150ml heavy walled glass vessel, capable of operating at more than 600 kPascals (the mix vessel) connected 20 to a second identical vessel (the loading vessel) such that liquid in the mix vessel can be transferred into the loading vessel. Include valves and fittings in suitable places to allow complete evacuation of the system, charging of solvent (TFE) to the mix vessel, and the transferring of solvent from the mix vessel to the loading vessel. Charge 0.1g of nicotine with an 25 assay greater than 95% to the mix vessel, and 10g of a dried, powder form, styrenic strongly acidic cation exchange resin with a sulfonic acid functionality with weight capacity of 4.3 to 4.9 meq/g(such as Amberlite® IRP69 available from Rohm and Haas Company, Philadelphia, Pennsylvania) to the loading vessel. Evacuate the equipment to remove 30 the air and then charge 50g of solvent (TFE) to the mix vessel. The pressure will rise to about 520 kPascals due to the vapor pressure of TFE.

Stir the TFE and nicotine for 5 minutes to dissolve said nicotine and then transfer the solution to the loading vessel. Mix the slurry in the loading vessel for 18 hours and then reduce the pressure in the loading vessel by venting it to the atmosphere to remove the TFE. The remaining dry solid  
5 is nicotine loaded onto the cation exchange resin.

EXAMPLE 11—Immiscible Solvent Loading Of A Water Soluble Active

Use commercial scale equipment that allows the same operations as described in Example 1, with the addition of a compressor connected to the  
10 receiver, a condenser attached to the outlet of the compressor, and a suitable pressure vessel for storage of TFE. Charge 18kg of nicotine that meets the purity requirements of the US Pharmacopeia 24, and charge 100kg of a methacrylic weakly acidic cation exchange resin with a carboxylic acid functionality with weight capacity of 10.1 to 11.1 meq/g  
15 (such as Amberlite® IRP64 available from Rohm and Haas Company) to the loading vessel. Evacuate the equipment to remove the air. Seal the equipment to prevent entry of air, and then charge 360kg of TFE to the mixing vessel. Mix the nicotine and TFE for 15 minutes to dissolve the nicotine, and then transfer the solution to the loading vessel. Mix the  
20 slurry for at least 8 hours to allow the nicotine to be absorbed by the resin. Reduce the pressure in the loading vessel to 350 kPascals by operating the compressor. The TFE will distill into the compressor. Provide heat to maintain the loading vessel at 15°C. Operate the compressor to achieve >520 kPascals at the outlet, and operate the condenser to cool the  
25 compressed TFE to 15-20°C. When all the TFE has evaporated remove the resin loaded with nicotine (118 Kg) from the vessel.

CLAIMS

1. A method for preparing a resinate comprising the steps of:
  - a. blending a poorly water soluble active substance with a resin and a solvent selected from the group consisting of water, a water miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;
  - b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.
2. A method for preparing a resinate comprising steps of:
  - a. blending a water soluble active substance with a resin and a solvent selected from the group consisting of a water miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;
  - b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.
3. A method according to Claim 1, wherein the poorly water soluble active substance is selected from the group consisting of indomethacin, nelfinavir, and midazolam.
4. A method according to Claim 3, wherein the solvent is a water immiscible solvent.

5. A method according to Claim 4, where in the active substance is loaded at 5-100% of the ion exchange capacity of the resin.
6. A method according to Claim 2, where in the water soluble active  
5 substance is nicotine.
7. A method according to Claim 6, wherein the solvent is a water immiscible solvent .
- 10 8. A method according to Claim 7, where in the active substance is loaded at 100% of the ion exchange capacity of the resin.
9. A method according to claim 1 or claim 2, wherein said active substance is a naturally occurring or a synthetic material.
- 15 10. A method according to claim 9, wherein said active substance is selected from nutraceuticals, biologically active extracts of botanical materials, flavours and fragrances.
- 20 11. A method according to any of claims 1, 2, 9 or 10, wherein said solvent comprises a C<sub>1</sub> to C<sub>4</sub> fluorinated hydrocarbon.
12. A method according to claim 11, wherein said fluorinated hydrocarbon includes carbon, fluorine and hydrogen atoms only.
- 25 13. A method according to claim 11, wherein said fluorinated hydrocarbon is tetrafluoroethane.
14. A method according to any preceding claim, which includes separating  
30 a resinate comprising active substance/resin from solvents after step b.

15. A method of preparing a resinate comprising the steps of:

- (a) blending an active substance with a resin and a solvent to form an active substance/resin/solvent mixture; and
- 5 (b) separating a resinate comprising active substance/resin from solvents.

16. A method according to claim 15, wherein said solvent is a fluorinated hydrocarbon solvent.

10

17. A method according to any preceding claim, wherein, in the method, at least 0.5kg of active substance is blended with solvent in step a.

15

18. A resinate comprising an active substance in combination with a resin, wherein the resinate includes a trace of a fluorinated hydrocarbon solvent.

20

19. A formulation comprising a resinate prepared in the method according to any of claims 1 to 17 or as described in claim 18, wherein the formulation includes at least 0.25 wt% of resinate.

20. A formulation according to claim 19 which comprises said resinate in combination with another solid or liquid.

25

21. A method of preparing a formulation which comprises contacting a resinate prepared in a method according to any of claims 1 to 17 or being as described in any of claims 18 to 20 with another solid or liquid.

## INTERNATIONAL SEARCH REPORT

PCT/GB 02/00199

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBASE, BIOSIS, EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	IRWIN W J ET AL: "DRUG-DELIVERY BY ION-EXCHANGE. PART VII: RELEASE OF ACIDIC DRUGS FROM ANIONIC EXCHANGE RESINATE COMPLEXES" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 16, no. 6, 1990, pages 883-898, XP001029685 ISSN: 0363-9045 abstract ---	1-21
E	EP 1 190 721 A (ROHM & HAAS) 27 March 2002 (2002-03-27) column 4, line 48 -column 5, line 3; claims 1,3,10 --- -/-	1-21

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search | Date of mailing of the International search report

2 October 2002

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## INTERNATIONAL SEARCH REPORT

PCT/GB 02/00199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	EP 1 175 914 A (ROHM & HAAS) 30 January 2002 (2002-01-30) claims; examples 1-3,7 ----	1-21
E	EP 1 175 915 A (ROHM & HAAS) 30 January 2002 (2002-01-30) claims 1,10; examples 1,2,7 -----	1-21

**INTERNATIONAL SEARCH REPORT**

PCT/GB 02/00199

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02 00199

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

### Continuation of Box I.2

Present claims 1-21 relate to an extremely large number of possible compounds or methods. In fact, the claims contain so many options, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely compounds or methods have been searched recited in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

PCT/GB 02/00199

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 1190721	A 27-03-2002	EP 1190721 A2 JP 2002114682 A US 2002015687 A1		27-03-2002 16-04-2002 07-02-2002
EP 1175914	A 30-01-2002	EP 1175914 A2 JP 2002060350 A US 2002032245 A1		30-01-2002 26-02-2002 14-03-2002
EP 1175915	A 30-01-2002	EP 1175915 A1 JP 2002053495 A US 2002031490 A1		30-01-2002 19-02-2002 14-03-2002